Estimating Lifetime Benefits of Comprehensive Disease-Modifying Pharmacologic Therapies in Heart Failure with Reduced Ejection Fraction

Running Title: Comprehensive Disease-Modifying Therapies in HFrEF

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PARADIGM-HF (Prospective Comparison of ARNI [Angiotensin Receptor–Neprilysin Inhibitor] with ACEI [Angiotensin-Converting–Enzyme Inhibitor] to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial): NCT01035255
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Research in Context

Evidence before this study

Patients with heart failure with reduced ejection (HFrEF) experience substantially shorter life expectancies compared with persons in the general population of similar age. Multiple therapies are now known to individually extend survival in chronic HFrEF. While most patients are currently treated with renin-angiotensin-system inhibitors (RASi) and β-blockers, three drug classes (ARNI, MRA, SGLT2i) have additionally been shown to reduce mortality in HFrEF beyond these previously established core elements. Real-world data have highlighted incomplete use of these more recent additions to the therapeutic armamentarium.

Added value of this study

Leveraging data from 3 contemporary randomized clinical trials in chronic HFrEF, we estimate that comprehensive disease-modifying pharmacologic therapy (ARNI+β-blocker+MRA+SGLT2i) reduces the hazard of cardiovascular death or HF hospitalization by 62% (HR 0.38; 95% CI 0.30-0.47) compared with limited conventional therapy (ACEi/ARB+β-blocker). Depending on the age of therapeutic optimization, treatment with comprehensive disease-modifying pharmacologic therapy was estimated to afford 1.4 to 6.3 additional years alive and 2.7 to 8.3 additional years free from cardiovascular death or HF hospitalization compared with treatment with ACEi/ARB+β-blocker alone.

Implications of all the available evidence

Compared with limited conventional neurohormonal medical therapies commonly used in clinical practice, these data support the central role of comprehensive disease-modifying pharmacologic therapy to halt or delay clinical progression and extend survival in HFrEF. Given incomplete uptake of well-established and novel therapies, innovative and disruptive implementation strategies are urgently needed to facilitate use of combination multi-drug regimens in appropriately selected patients with HFrEF. The survival benefits estimated with comprehensive disease-modifying pharmacologic therapy may be important in shared therapeutic decision-making and future health system valuation.

Summary

Background

Three drug classes (mineralocorticoid receptor antagonists [MRA], angiotensin receptor-neprilysin inhibitors [ARNI], and sodium glucose cotransporter-2 inhibitors [SGLT2i]) have been shown to reduce mortality in heart failure with reduced ejection fraction [HFrEF] beyond angiotensin-converting enzyme inhibitors/angiotensin receptor blockers [ACEi/ARB] and β-blockers. However, each class was studied with variable background therapy and the expected treatment benefits with their combined use are not known.

Methods

We estimated treatment effects of comprehensive disease-modifying pharmacologic therapy (ARNI+β-blocker+MRA+SGLT2i) vs. limited conventional therapy (ACEi/ARB+ β-blocker) in chronic HFrEF by making indirect comparisons of pivotal trials. Treatment estimates were derived from EMPHASIS-HF (n=2,737), PARADIGM-HF (n=8,399), and DAPA-HF (n=4,744). Assuming these relative treatment effects are consistent over time, we then projected potential incremental long-term survival gains with comprehensive disease-modifying therapy in the control arm of the EMPHASIS-HF trial (which required use of ACEi/ARB+β-blocker, unless contraindicated).

Findings

The imputed aggregate treatment effects of comprehensive disease-modifying therapy vs. ACEi/ARB+β-blocker on cardiovascular death or HF hospitalization was 62% (HR 0.38; 95% CI 0.30-0.47). Reductions in hazard of cardiovascular death alone, HF hospitalization alone, and all-cause mortality were 50% (HR 0.50; 95% CI 0.37-0.67), 68% (HR 0.32; 95% CI 0.24-0.43), and 47% (HR 0.53; 95% CI 0.40-0.70), respectively. Based on the 16% annualized event rate of cardiovascular death or HF hospitalization in the control arm of EMPHASIS-HF, the range of aggregate treatment effects would translate to an estimated absolute risk reduction with comprehensive disease-modifying therapy of 18-25% over 3 years with a corresponding number-needed-to-treat of 4 to 6. Treatment with comprehensive disease-modifying pharmacologic therapy was estimated to afford 2.7 additional years (for an 80-year old) to 8.3 (for a 55 year-old) additional years free from cardiovascular death or HF hospitalization and 1.4 additional years (for an 80-year old) to 6.3 (for a 55 year-old) additional years alive compared with limited conventional medical therapy with ACEi/ARB+β-blocker alone.

Interpretation

Among patients with HFrEF, the anticipated aggregate treatment effects of early comprehensive disease-modifying pharmacologic therapy are substantial and may extend survival and event-free survival by up to 6 years and 8 years, respectively.

Funding

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Introduction

Patients with heart failure with reduced ejection (HFrEF) experience substantially shorter life expectancies compared with persons in the general population of similar age.[1,2] Over the last 3 decades, there have been stepwise advancements in pharmacotherapy for patients with HFrEF. While most patients are currently treated with renin-angiotensin-system inhibitors (RASi) and β-blockers,[3–5] three drug classes have additionally been shown to reduce mortality in HFrEF beyond these previously established core elements. Trials have demonstrated clinical superiority of mineralocorticoid receptor antagonists (MRA)[6,7] and sodium-glucose cotransporter-2 inhibitors (SGLT2i)[8] when each was tested against a placebo control in addition to standard care inclusive of RASi and β-blockers (as tolerated). In addition, the angiotensin receptor-neprilysin inhibitor (ARNI), sacubitril/valsartan, has been shown to be superior when directly tested against an angiotensin-converting enzyme inhibitor (ACEi) in improving clinical outcomes.[9] Real-world data have highlighted incomplete use of these more recent additions to the therapeutic armamentarium, even among patients deemed clinically eligible without apparent contraindication or documented intolerance. For instance, despite class I guideline recommendations, use of MRAs (33.7% to 35.7%) and ARNI (13.6% to 19.8%) in eligible patients remains suboptimal. Similarly, although it has been over 4 years since clinical trials have demonstrated benefits of SGLT2i in high-risk patients with type 2 diabetes, only 2% of HFrEF patients with comorbid diabetes are currently being treated with SGLT2i in clinical practice.[3–5,10,11] These gaps in evidence-based medical therapies have been implicated in relatively stagnant mortality trajectories of patients living with HFrEF.[12]

Communication of the estimated treatment benefits of comprehensive disease-modifying pharmacologic therapy (ARNI, β-blocker, MRA, & SGLT2i) on clinical outcomes, especially if used over a lifetime, may facilitate decision-making by patients, clinicians, health systems, and payers. We first estimated anticipated *relative* treatment effects of comprehensive disease-modifying pharmacologic therapy vs. limited conventional therapy (ACEi/angiotensin receptor blocker (ARB)+β-blocker) in chronic HFrEF by making indirect comparisons of pivotal randomized clinical trials.[6,8,13] Using validated actuarial methods and assuming consistent treatment effects over time, we then project *absolute* survival gains with comprehensive disease-

modifying pharmacologic therapy if applied long-term, when compared with limited conventional therapies.

Methods

Relative Treatment Effects of Comprehensive Disease-Modifying Therapy. To estimate the effect of comprehensive disease-modifying pharmacologic therapy against previously established conventional therapy (ACEi/ARB+ β-blocker), we leveraged overall trial-level estimates from pivotal randomized clinical trials demonstrating the efficacy and safety of MRA,[6] ARNI,[13] & SGLT2i.[8] Using established methods of indirect comparisons (commonly applied to assess treatment effects if a placebo was selected in an active-controlled trial),[14–17] we estimated combination effects of comprehensive disease-modifying therapy based on the product of treatment effects derived from each trial (**Supplemental Figure 1**). The 95% confidence interval (CI) was derived from square root of the sum of squared standard errors of the logarithmic hazard ratios (HR) across all 3 comparisons. All trials required background therapy (as tolerated) with RASi+β-blocker. As the use of MRA and ARNI was variable in these trials, we derived *conservative* estimates of the aggregate treatment effects by additionally assessing treatment effects in key subgroups treated with these therapies at baseline.

EMPHASIS-HF. From 2006 to 2010, EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure)[6] randomized 2,737 patients over the age of 55 years with chronic HFrEF (≤30% or ≤35% with prolonged QRS duration) with New York Heart Association (NYHA) class II symptoms to eplerenone 25-50mg once daily or matching placebo. All patients were required to be on maximally tolerated ACEi/ARB and a β-blocker at baseline. Median duration follow-up was 21 months.

PARADIGM-HF. From 2009 to 2012, PARADIGM-HF (Prospective Comparison of ARNI with ACEI to Determine Impact on Global Mortality and Morbidity in Heart Failure Trial)[13] enrolled 10,521 patients at least 18 years of age with HFrEF (≤40%; changed to ≤35% by protocol amendment) and NYHA functional class II-IV. Patients tolerating sequential single-blind run-in phases with target doses of enalapril and sacubitril/valsartan (n=8,399) were randomized to enalapril 10mg twice daily or sacubitril/valsartan 200mg twice daily. Treatment

with stable doses of ACEi/ARB+β-blocker for at least 4 weeks was required by trial protocol. Median follow-up was 27 months.

DAPA-HF. From 2017 to 2018, DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure)[8] randomized 4,744 patients who were age ≥18 years with chronic HFrEF (≤40%) and NYHA class II-IV symptoms to dapagliflozin 10mg once daily or matching placebo. Patients with and without diabetes mellitus were evaluated. In sensitivity analysis, we evaluated the effects of SGLT2i when used in a combination regimen by leveraging subgroup data from patients at baseline who were treated with ARNI (n=508; 11%). Median follow-up was 18 months.

Clinical Outcomes. The primary endpoint for the current analysis was composite of cardiovascular death or first HF hospitalization. Additional endpoints of interest included each of the components of this composite and all-cause mortality.

Estimating Gains in Event-Free Survival and Overall Survival. We then simulated event-free survival and overall survival by applying the treatment effects of comprehensive disease-modifying pharmacologic therapy (as estimated above) to the control arm of the EMPHASIS-HF trial. We used previously validated actuarial (age-based) methods[18] to calculate non-parametric Kaplan-Meier estimates of survival free from a primary endpoint and overall life expectancy at every year of age among patients in control arm of the EMPHASIS-HF trial.[19] This method uses age (at baseline and at the time of an event or death) as the time horizon rather than time from randomization. The area under the survival curve (up to a maximum of 90 years) reflected projected event-free survival and overall survival. Since age-treatment interactions have not been observed in each of the pivotal trials,[20–22] differences in survival curves reflect projected event-free survival and residual survival. For every age between 55 years (entry criteria for EMPHASIS-HF) and 80 years, we compared survival estimates of patients in the EMPHASIS-HF control arm as observed in the trial and as simulated if treated with comprehensive disease-modifying pharmacologic therapy. To estimate uncertainty around these survival gains, we additionally simulated survival under comprehensive medical therapy if the upper and lower bounds of the relative treatment effect were applied to the EMPHASIS-HF control arm.

Estimates of survival gains were smoothed with a locally weighted scatterplot smoothing (LOWESS) procedure.

Comparator Group of ACEi/ARB+β-blocker+MRA. We finally estimated the incremental effects of comprehensive pharmacological medical therapy (ARNI, β-blocker, MRA, & SGLT2i) if patients were already treated with ACEi/ARB+β-blocker+MRA. As a reference population, we used the eplerenone treatment arm of the EMPHASIS-HF trial (in which baseline use of ACEi/ARB+β-blocker as tolerated was protocol-specified and patients were randomly assigned to receive the MRA, eplerenone). To estimate the incremental effects of switching to ARNI and adding SGLT2i, we applied treatment estimates from subgroup data of those who were treated with an MRA at baseline in PARADIGM-HF (n=4,671; 56%) and DAPA-HF (n=3,370; 71%).

All participants provided written consent and the study protocol of each pivotal trial was approved by the institutional review board at each participating site. All analyses were performed using STATA, version 14.1 (StataCorp, College Station, TX). P-values<0.05 were considered statistically significant.

Role of the Funding Source. The trial sponsors had no role in the design, analysis, interpretation, writing of the manuscript, or decision to submit this post hoc analysis. The first author and the corresponding author were responsible for the decision to submit the manuscript.

Results

Relative Treatment Effects of Comprehensive Disease-Modifying Therapy. For the primary analysis, we analyzed trial-level estimates from EMPHASIS-HF (n=2,737), PARADIGM-HF (n=8,399), and DAPA-HF (n=4,744); **Table 1**. The imputed treatment effect of comprehensive disease-modifying pharmacologic therapy (with ARNI, β-blocker, MRA, & SGLT2i) vs. limited conventional therapy (with ACEi/ARB+β-blocker) on the primary endpoint of cardiovascular death or first HF hospitalization was 62% (HR 0.38; 95% CI 0.30-0.47); **Figure 1**. Reductions in hazard of cardiovascular death alone, HF hospitalization alone, and all-cause mortality were 50% (HR 0.50; 95% CI 0.37-0.67), 68% (HR 0.32; 95% CI 0.24-0.43), and 47% (HR 0.53; 95% CI 0.40-0.70), respectively (**Supplemental Figure 1**).

In sensitivity analysis, we substituted DAPA-HF overall treatment estimates with that derived from the subset of patients at baseline treated with ARNI (n=508; 11%). The estimated treatment effects of comprehensive disease-modifying pharmacologic therapy on the primary endpoint was similar: HR 0.39; 95% CI 0.25-0.61.

Absolute Event-Free and Total Survival Gains with Quadruple Therapy. We estimated survival in 1,373 patients in the placebo arm of EMPHASIS-HF. At baseline, an ACEi and/or ARB was used in 93% of patients and a β-blocker in 87%. Mean age was 68.6±7.6 years; 78% were men and 83% were white. Mean left ventricular ejection fraction (LVEF) was 26.1±4.7% and 53% had a prior history of HF hospitalization.

Over median follow-up of 20.5 (9.5-32.5) months, 356 primary endpoints (25.9%; 16.4[14.8-18.2] per 100 patient-years) and 213 deaths (15.5%; 8.9[7.8-10.2] per 100 patient-years) occurred in the control arm of EMPHASIS-HF. Based on the annualized event rate of cardiovascular death or HF hospitalization in the control arm of EMPHASIS-HF, the range of aggregate treatment effects would translate to an estimated absolute risk reduction with comprehensive disease-modifying pharmacologic therapy of 18-25% over 3 years with a corresponding number-needed-to-treat of 4 to 6 in the prevention of a primary endpoint. With respect to mortality, absolute risk reductions were estimated to range between 6-13% over 3 years with a number-needed-to-treat of 8 to 16 in the prevention of 1 death.

At age 55, the estimated survival free from a primary endpoint was 14.7 years with comprehensive disease-modifying pharmacologic therapy and 6.4 years with ACEi/ARB+β-blocker (difference: 8.3 years; 95% CI 6.2-10.7 years); **Figure 2**. At age 55, the estimated overall residual survival was 17.7 years with comprehensive disease-modifying pharmacologic therapy and 11.4 years with ACEi/ARB+β-blocker (difference: 6.3 years; 95% CI 3.4-9.1 years); **Figure 3**. Given that baseline life expectancies varied by age, we further estimated absolute survival gains across a broad range of ages (55 to 80 years); **Figure 4**. Treatment with comprehensive disease-modifying pharmacologic therapy was estimated to afford 2.7 additional years (for an 80-year old) to 8.3 (for a 55 year-old) additional years free from a primary endpoint and 1.4 additional years (for an 80-year old) to 6.3 (for a 55 year-old) additional years alive compared with limited conventional medical therapy with ACEi/ARB+β-blocker alone.

Comparator Group of ACEi/ARB+β-blocker+MRA. If ACEi/ARB+β-blocker+MRA was selected as the comparator, further therapeutic optimization by switching to ARNI & adding SGLT2i would be expected to reduce the hazard of the primary endpoint by 36% (HR 0.64; 95% CI 0.52-0.78). Comprehensive disease-modifying therapy would be estimated to yield 1.2 to 4.1 additional years free from the primary endpoint and 0.8 to 3.1 years alive compared with treatment with ACEi/ARB+β-blocker+MRA.

Discussion

A central goal of HF therapeutics is to safely prevent or postpone morbidity-free survival. In HFrEF, multiple therapeutic advances have offered promise in delaying clinical progression and extending disease-free survival. Combination therapy with ARNI, β-blocker, and MRA represents the current guideline-recommended therapeutic standard in HFrEF. In light of robust and favorable clinical trial data, the addition of SGLT2i in a comprehensive regimen is poised to be adopted in clinical practice guidelines. Comprehensive disease-modifying pharmacologic therapies (inclusive of 4 pills, but 5 distinct drugs) now target multiple mechanistic pathways beyond conventional neurohormonal therapies (ACEi/ARB+β-blocker). While these therapies have been individually investigated in rigorously conducted randomized clinical trials, the aggregate effects on clinical outcomes of their combined use had not been directly defined.

Adequately powered trials evaluating the long-term clinical effects of various therapeutic combinations may be challenging to conduct with traditional approaches. As such, we applied established methods available to first estimate the relative treatment effects of comprehensive disease-modifying pharmacologic therapy and then to forecast these benefits on long-term survival. ACEi/ARB+β-blocker therapy alone has been previously estimated to lower hazards of death by 43-53% vs. placebo in historical randomized clinical trials.[23] When compared with this previously established treatment regimen widely administered in clinical practice,[3–5] we estimate that optimization with comprehensive disease-modifying pharmacologic therapy would be expected to further lower cardiovascular death or HF hospitalization by over 60%. Over 3 years, the estimated absolute risk reduction was 18-25% with a number-needed-to-treat to prevent 1 event of only 4 to 6. With lifetime use, assuming consistent treatment benefits, these exploratory actuarial analyses suggest potential event-free survival gains of up to 8 years and absolute

survival gains of up to 6 years. Even among patients who are already treated with ACEi/ARB+β-blocker+MRA therapy (an evidence-based, guideline-supported strategy that remains underutilized), we estimate substantial survival benefits with further optimization with switching to an ARNI and adding an SGLT2i. Younger patients with HFrEF, who would be anticipated to have longer projected survival and treatment duration, stand to benefit the most from survival gains related to comprehensive disease-modifying pharmacologic therapy. Yet, for all age groups analyzed meaningful gains in life-years were projected. These summary data serve as a testament to the tremendous progress in understanding optimal treatment approaches to chronic HFrEF garnered from clinical trials conducted over the last 3 decades.

Each pivotal randomized clinical trial of medical therapy for HFrEF was conducted sequentially during different eras, and as such, we evaluated the best available data (including subgroups fully treated on background therapies). While these data do suggest substantial benefits with early combination therapy, these do not inform a specific therapeutic sequence or pathway for prioritizing initiation. For instance, although EMPHASIS-HF was conducted prior to PARADIGM-HF, early switching of ACEi/ARB to ARNI may facilitate subsequent integration of MRA, due to lower attendant risks of hyperkalemia.[24] Conversely, blood pressure lowering with upstream integration of ARNI may preclude subsequent dose titration or initiation of other disease-modifying therapies. Similarly, while DAPA-HF mostly recently demonstrated the therapeutic potential of SGLT2i in HFrEF, earlier use of SGLT2i in therapeutic pathways, prior to ARNI or MRA, may still be safe and effective. The largely non-overlapping posited mechanisms of benefit, routes of metabolism, and adverse event profiles argue that both ARNI and SGLT2i should be rapidly integrated into clinical care of HFrEF, irrespective of specific order of initiation.

Accumulating data have suggested that clustered or near-simultaneous initiation and rapid uptitration of guideline-directed medical therapies are feasible and safe, either under the guidance of structured ambulatory programs or in hospitalized settings.[25] Once these therapies become broadly available and generic, a polypill of comprehensive disease-modifying therapy may be feasibly implemented to promote effective and equitable therapy at the population level.[26] While these analyses support the aggregate efficacy of combination, comprehensive

disease-modifying pharmacologic therapy, these data do not inform other practical aspects that may influence decision-making around its implementation. Multi-drug regimens increase the potential for non-adherence, partially related to incremental out-of-pocket expenditures and therapeutic complexity. These analyses also do not dissect potential safety issues related to comprehensive therapy. However, data from pivotal clinical trials have added reassurance that optimizing therapeutic regimens can be done safely with appropriate follow-up and monitoring. For instance, in PARADIGM-HF, sacubitril/valsartan resulted in less hyperkalemia and renal insufficiency compared with enalapril when added to background MRA therapy.[24] Similarly, there were low rates of drug discontinuation or serious adverse events with addition of dapagliflozin to excellent background medical therapy in DAPA-HF, and these risks were comparable to those observed with placebo.[8] However, understanding tolerability and safety of comprehensive disease-modifying therapy with real-world use is of high priority. Parallel efforts to advance implementation science are needed to complement clinical trial evidence to promote optimal use of therapies at target doses among patients with HFrEF.

Traditional reporting of treatment effects in clinical trials (such as a HR) is often challenging to communicate to patients and clinicians. Reductions in potential future events may be difficult to conceptualize given the lack of a reference.[27] Given the chronicity of HF and since trials are typically conducted over a time course shorter than the life expectancy of a patient, projections of lifetime application of a given therapy beyond the duration of the trial may better frame its anticipated long-term benefits. We developed and validated actuarial methods using clinical trial data to estimate residual lifespan.[18] Our estimates of average survival are congruent with previously published age-specific life expectancy in HF. We estimated that a 55-year old in EMPHASIS-HF would live on average for 11.4 years; a previous population-based cohort study from Canada similarly estimated average survival of patients with HFrEF aged 50-60 years to be 11.3± 3.3 years.[2] Estimation of life expectancy and quantification of potential survival gains with a given intervention may facilitate medical decision-making. Communication of the substantial survival gains free from clinical events may encourage initiation and adherence to combination, comprehensive disease-modifying pharmacologic medical therapy.

The analytic methods employed have important assumptions and limitations. First, we assume that adherence to therapies and treatment benefits observed during short duration trial follow-up would be expected to persist long-term. However, greater nonadherence, especially considering use of multiple therapies, may be expected in usual care settings, which would in turn attenuate these projected survival gains. Furthermore, it is uncertain whether clinical benefits of these therapies continue to accrue over lifetime exposure. Second, these methods may overestimate the expected aggregate effects as we assume additive benefits. It is plausible that the composite benefits of combination regimens may be partially attenuated due to overlapping mechanistic pathways. To address this, we conducted sensitivity analyses using subgroup data of patients treated with various background therapies, which yielded consistent findings. Third, the trials analyzed in this study were conducted over different time frames with variable populations, clinical risk, and background therapies. However, as we strictly only considered treatment effect estimates derived from randomized comparisons *within* trials, these factors were assumed to be balanced between treatment arms (as a function of randomization). Furthermore, we only considered relative (rather than absolute) treatment effects as these may be more comparable across trials. Fourth, our survival estimates may not be generalizable beyond the scope of these clinical trial populations. In this analysis, we attempted to provide population-level estimates of anticipated treatment effects. We did not evaluate variation in survival benefits by specific patient characteristics (such as race) due to small sample sizes which may produce unstable estimates and as primary trials detected limited treatment heterogeneity across key subgroups. However, individual patient factors are important to consider as comprehensive disease-modifying therapies are broadly applied. Fifth, we only included pharmacological therapies that have been shown to definitively improve survival in general cohorts of patients with HFrEF. We did not consider therapies that predominantly influence non-fatal HF events (such as digoxin and ivabradine), therapies that reduce mortality in specific subgroups (such as fixed-dose combination of isosorbide dinitrate plus hydralazine), and non-pharmacological therapies, including devices. Sixth, DAPA-HF was the first HF outcomes trial of SGLT2i to report; ongoing parallel investigations (NCT03057977) will further hone the effect estimates of SGLT2i as a class in HFrEF. Finally, our analyses focused on therapeutic benefits on key cardiovascular endpoints, including mortality, and did not account for potential adverse events or costs associated with use of comprehensive therapy. Despite these limitations, given that long-term

trials of comprehensive disease-modifying pharmacologic therapy are not available, these novel analyses from pivotal trials provide the best estimates of their potential combined therapeutic effects.

Compared with limited conventional neurohormonal medical therapies commonly used in clinical practice, these data support the central role of comprehensive disease-modifying pharmacologic therapy to halt or delay clinical progression and extend survival in HFrEF. Given incomplete uptake of well-established and novel therapies, innovative and disruptive implementation strategies are urgently needed to facilitate use of combination multi-drug regimens in appropriately selected patients with HFrEF. The survival benefits estimated with comprehensive disease-modifying pharmacologic therapy may be important in shared therapeutic decision-making and future health system valuation.

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Contributors

MV, BLC, & SDS conceived of and designed the study. MV, BLC, & JPF did the analysis. MV drafted the manuscript. All authors contributed to data interpretation and writing of the final version of the manuscript.

Declaration of Interests

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Data Sharing

All trial sponsors are committed to sharing access to patient-level data and supporting clinical documents from eligible studies. The trial data availability is according to the criteria and processes described.[28–30]

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None

Figure Legends

Figure 1. Estimation of Relative Treatment Effects of Comprehensive Disease-Modifying Pharmacologic Therapy on Key Cardiovascular Events

This putative analysis estimates the treatment effects of comprehensive disease-modifying pharmacologic therapy compared with angiotensin-converting enzyme inhibitor (ACEi)/angiotensin receptor blocker (ARB)+β-blocker by making indirect comparisons of pivotal trials in heart failure (HF).

Abbreviations = ARNI = angiotensin receptor neprilysin inhibitor; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MRA = mineralocorticoid receptor antagonist; SGLT2i = sodium-glucose cotransporter-2 inhibitor.

Figure 2. Event-Free Survival with Comprehensive Disease-Modifying Therapy (ARNI+β-blocker+MRA+SGLT2i) vs. Limited Conventional Therapy (ACEi/ARB+β-blocker)

Age-based Kaplan–Meier estimated curves are displayed for patients at age 55 years (**A**) and 65 years (**B**) for survival free from the primary endpoint, cardiovascular death or heart failure hospitalization. The control arm of the EMPHASIS-HF (Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure) who were required to be on maximally tolerated ACEi/ARB+β-blocker therapy served as the reference group (red). The comparator was a simulated group by applying the estimated treatment effects of comprehensive therapy to the control arm of the EMPHASIS-HF trial (grey). Residual event-free survival was estimated using the area under the survival curve up to a maximum of 90 years.

Abbreviations = ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; MRA = mineralocorticoid receptor antagonist; SGLT2i = sodium-glucose cotransporter-2 inhibitor.

Figure 3. Long-Term Survival with Comprehensive Disease-Modifying Therapy (ARNI+β-blocker+MRA+SGLT2i) vs. Limited Conventional Therapy (ACEi/ARB+β-blocker)

Age-based Kaplan–Meier estimated curves are displayed for patients at age 55 years (**A**) and 65 years (**B**) for survival. Residual lifespan was estimated using the area under the survival curve up to a maximum of 90 years. Methods and abbreviations as per Figure 2.

Figure 4. Treatment Benefits on Overall Survival and Event-Free Survival with Comprehensive Disease-Modifying Therapy (ARNI+β-blocker+MRA+SGLT2i) vs. Limited Conventional Therapy (ACEi/ARB+β-blocker)

Estimated mean event-free survival times (**A**) and overall survival times (**B**) in the EMPHASIS-HF control arm and the simulated comprehensive therapy group for every age between 55 and 80 years. Treatment differences and 95% confidence intervals (CI) are estimated for mean event-free survival (**C**) and overall survival (**D**) after application of a locally weighted scatterplot smoothing procedure. The dashed lines represent survival gains if the upper and lower bounds of the relative treatment effect are applied as the simulated comprehensive therapy group. Abbreviations as per Figure 1.

Table 1. Key Baseline Characteristics & Background Medical Therapy

		EMPHASIS-HF (n=2,737)	PARADIGM-HF (n=8,399)	DAPA-HF (n=4,744)
Comparison		Eplerenone vs. Placebo	Sacubitril/Valsartan vs. Enalapril	Dapagliflozin vs. Placebo
Enrollment Period		2006-2010	2009-2012	2017-2018
Median Follow-up (months)		21	27	18
Age (years)		69 ± 8	64 ± 11	66 ± 11
Women		610 (22%)	1832 (22%)	1109 (23%)
Systolic blood pressure (mmHg), mean±SD		124±17	121 ± 15	122 ± 16
Heart rate (bpm), mean±SD		72±13	72 ± 12	72 ± 12
Left ventricular ejection fraction (%), mean±SD		26 ± 5	30 ± 6	31 ± 7
New York Heart Association Class				
	1	0 (0%)	389 (5%)	0 (0%)
	2	2737 (100%)	5919 (71%)	3203 (68%)
	3	0 (0%)	2018 (24%)	1498 (32%)
	4	0 (0%)	60 (1%)	43 (1%)
Atrial fibrillation		844 (31%)	3091 (37%)	1818 (38%)
Diabetes mellitus		859 (31%)	2907 (35%)	1983 (42%)
Prior hospitalization for HF		1440 (53%)	5274 (63%)	2251 (47%)
Diuretics		2326 (85%)	6738 (80%)	4433 (93%)
ACEi/ARB/ARNI*		2557 (93%)	8379 (100%)	4442 (94%)
β-blocker		2374 (87%)	7811 (93%)	4558 (96%)
MRA		--	4671 (56%)	3370 (71%)

***** DAPA-HF is the only trial that enrolled patients on background ARNI (n=508)

Abbreviations: ACEi = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; HF = heart failure; MRA = mineralocorticoid receptor antagonist; SD = standard deviation

584 **Figure 1.**
585

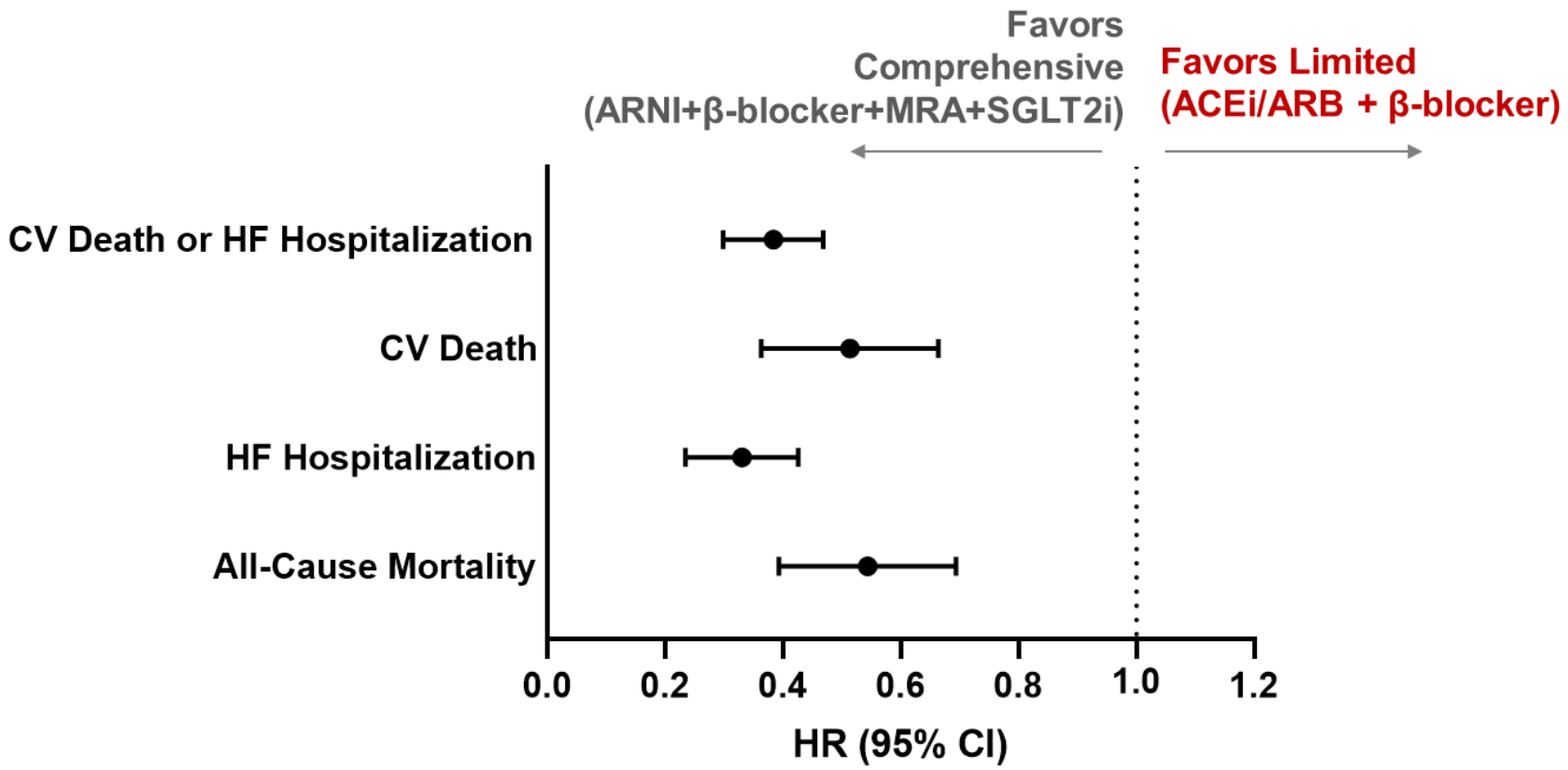
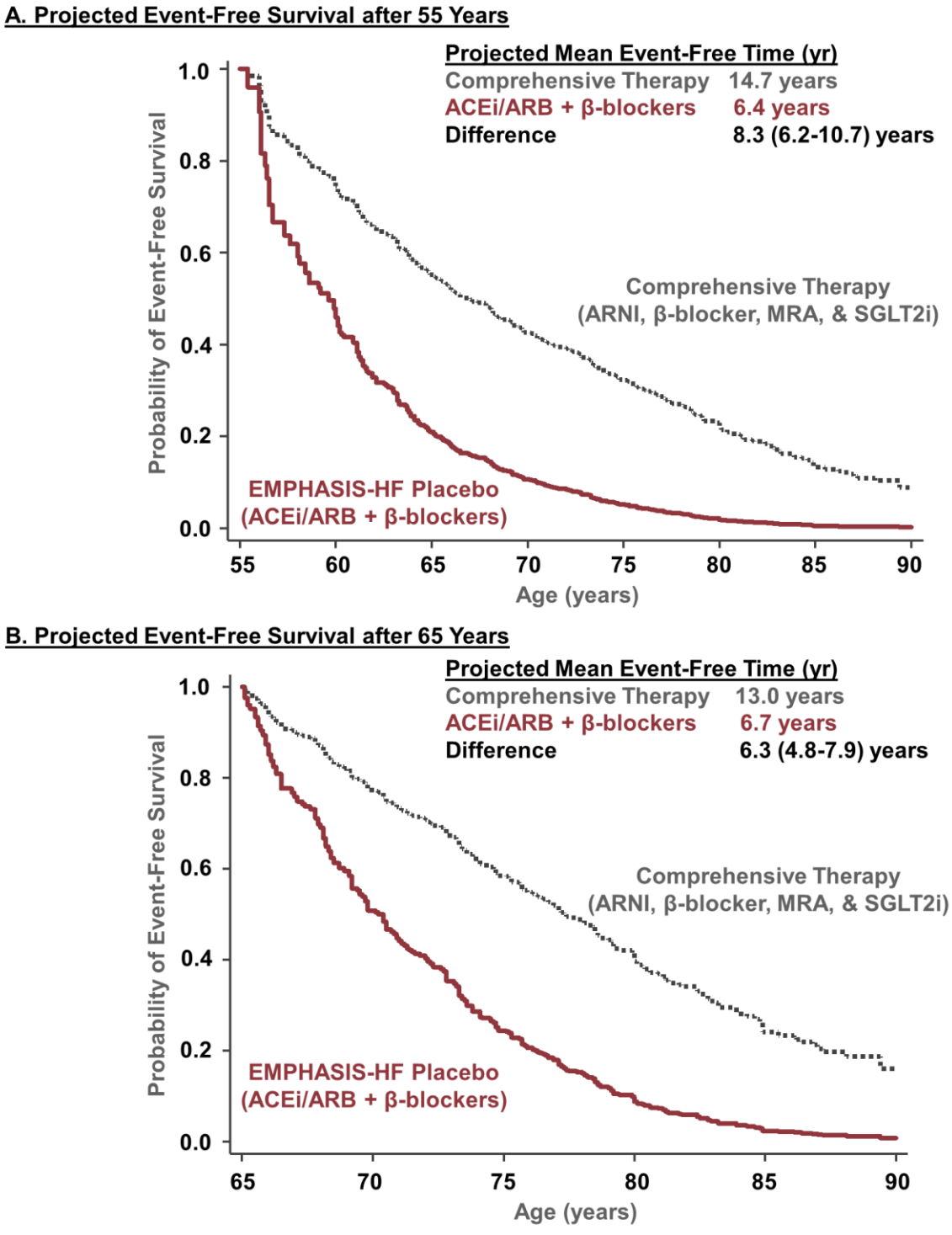


Figure 2.


A. Projected Event-Free Survival after 55 Years
Projected Mean Event-Free Time (yr)
Comprehensive Therapy 14.7 years
ACEi/ARB + β-blockers 6.4 years
Difference 8.3 (6.2-10.7) years
Comprehensive Therapy
(ARNI, β-blocker, MRA, & SGLT2i)
EMPHASIS-HF Placebo
(ACEi/ARB + β-blockers)
Probability of Event-Free Survival
1.0
0.8
0.6
0.4
0.2
0.0
55
60
65
70
75
80
85
90
Age (years)
B. Projected Event-Free Survival after 65 Years
Projected Mean Event-Free Time (yr)
Comprehensive Therapy 13.0 years
ACEi/ARB + β-blockers 6.7 years
Difference 6.3 (4.8-7.9) years
Comprehensive Therapy
(ARNI, β-blocker, MRA, & SGLT2i)
EMPHASIS-HF Placebo
(ACEi/ARB + β-blockers)
Probability of Event-Free Survival
1.0
0.8
0.6
0.4
0.2
0.0
65
70
75
80
85
90
Age (years)

588 **Figure 3.**

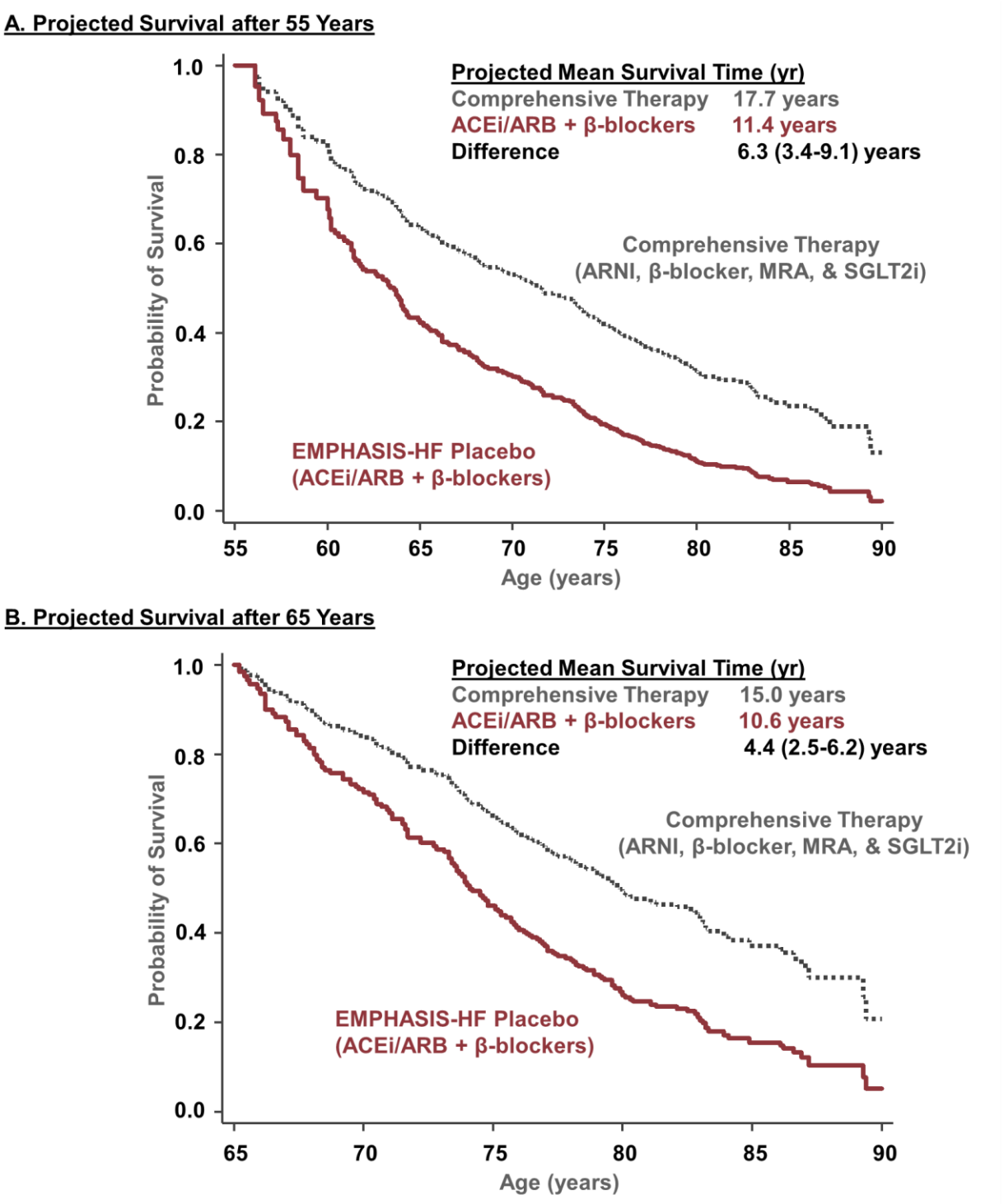
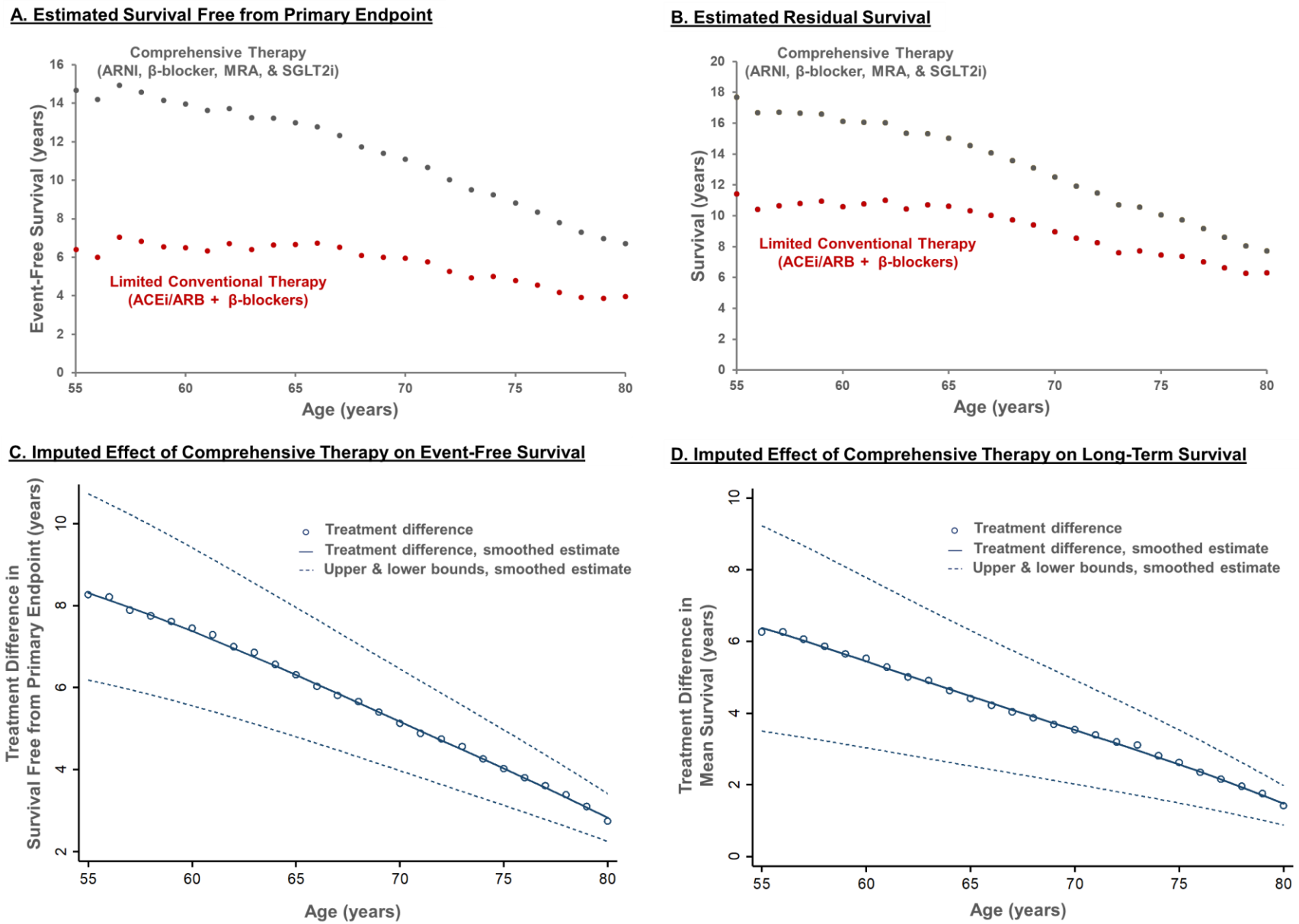
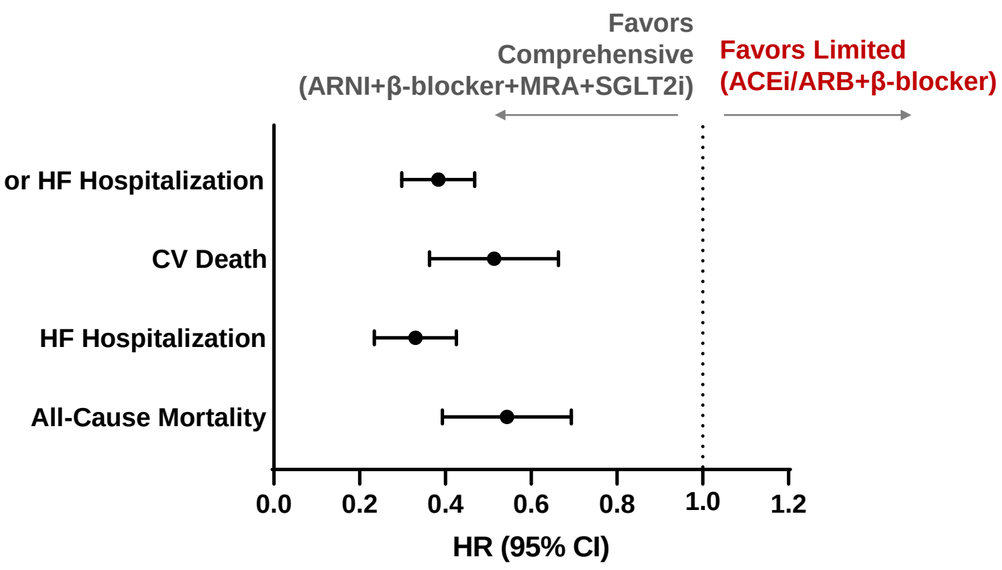
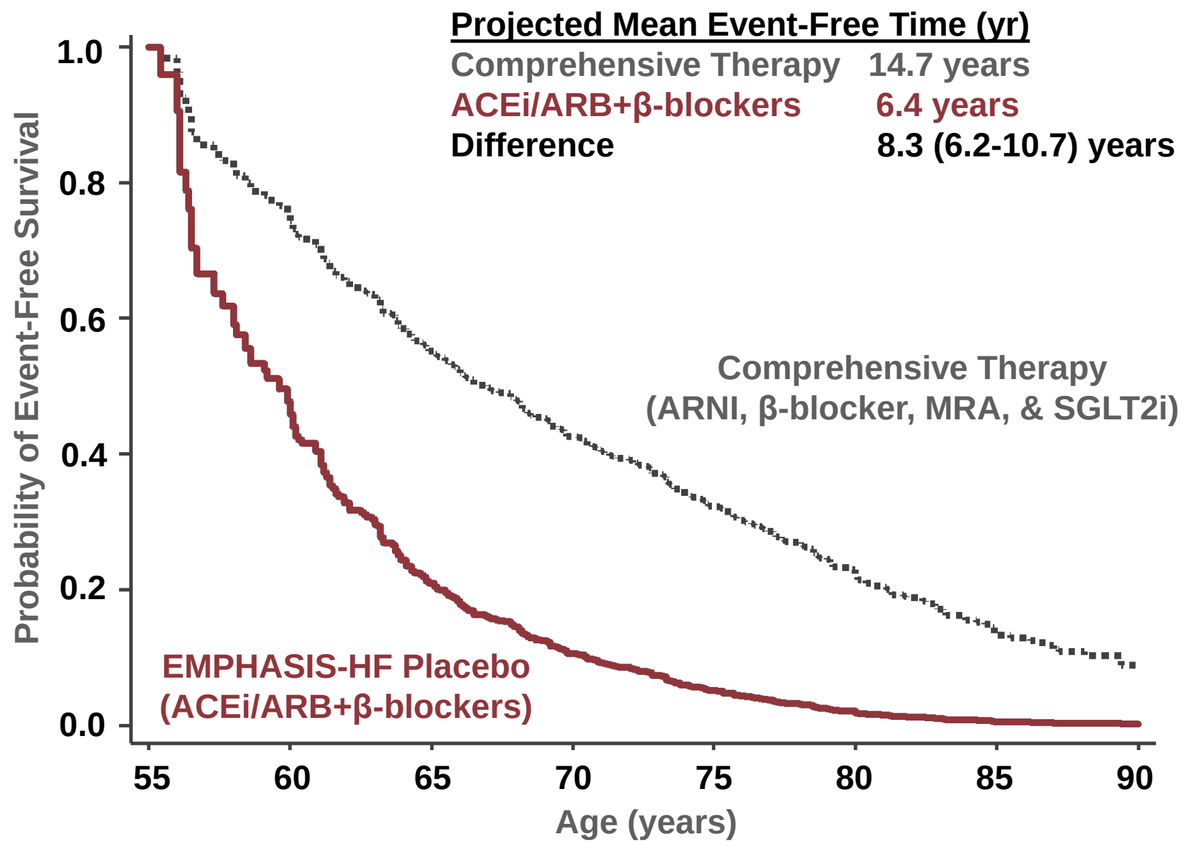

A. Projected Survival after 55 Years
Projected Mean Survival Time (yr)
Comprehensive Therapy 17.7 years
ACEi/ARB + β-blockers 11.4 years
Difference 6.3 (3.4-9.1) years
Comprehensive Therapy
(ARNI, β-blocker, MRA, & SGLT2i)
EMPHASIS-HF Placebo
(ACEi/ARB + β-blockers)
Probability of Survival
1.0
0.8
0.6
0.4
0.2
0.0
55
60
65
70
75
80
85
90
Age (years)
B. Projected Survival after 65 Years
Projected Mean Survival Time (yr)
Comprehensive Therapy 15.0 years
ACEi/ARB + β-blockers 10.6 years
Difference 4.4 (2.5-6.2) years
Comprehensive Therapy
(ARNI, β-blocker, MRA, & SGLT2i)
EMPHASIS-HF Placebo
(ACEi/ARB + β-blockers)
Probability of Survival
1.0
0.8
0.6
0.4
0.2
0.0
65
70
75
80
85
90
Age (years)

Figure 4.

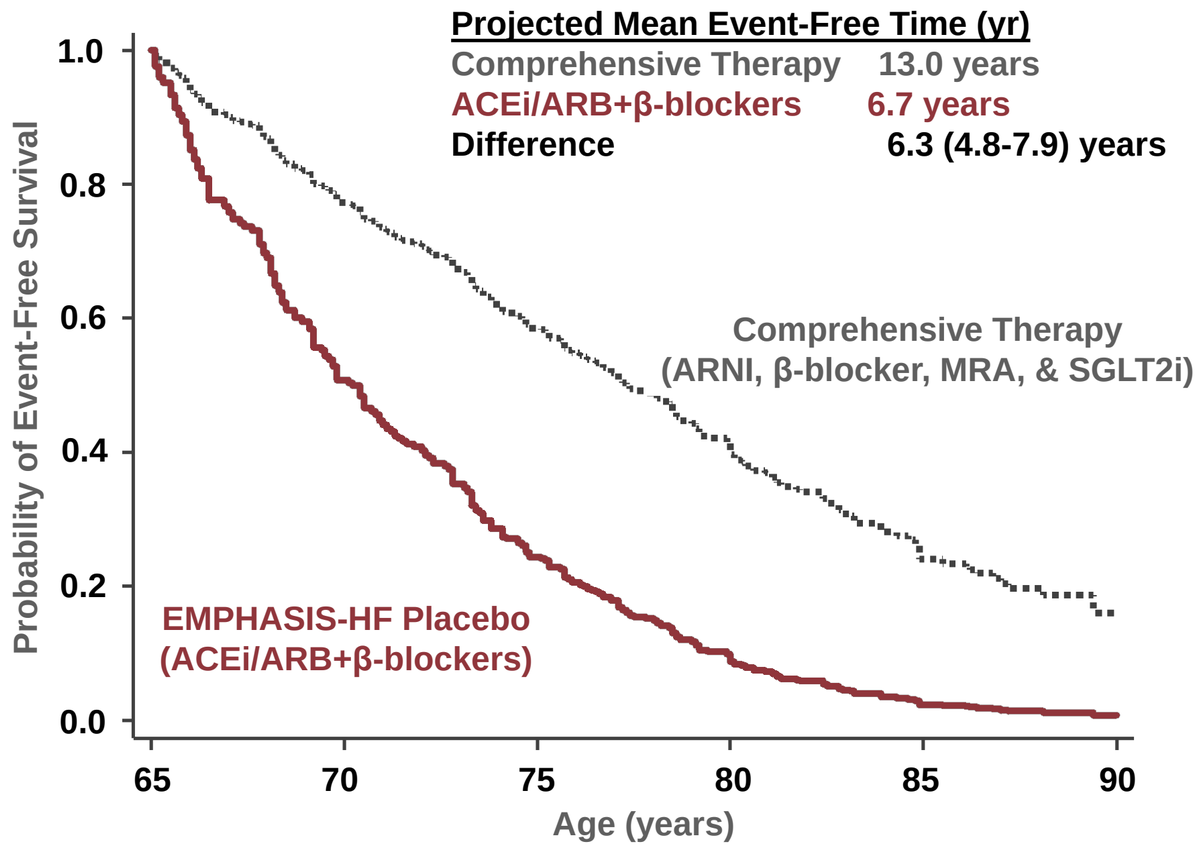

A. Estimated Survival Free from Primary Endpoint
Comprehensive Therapy
(ARNI, β-blocker, MRA, & SGLT2i)
Limited Conventional Therapy
(ACEi/ARB + β-blockers)
Event-Free Survival (years)
Age (years)
B. Estimated Residual Survival
Comprehensive Therapy
(ARNI, β-blocker, MRA, & SGLT2i)
Limited Conventional Therapy
(ACEi/ARB + β-blockers)
Survival (years)
Age (years)
C. Imputed Effect of Comprehensive Therapy on Event-Free Survival
Treatment difference
Treatment difference, smoothed estimate
Upper & lower bounds, smoothed estimate
Treatment Difference in Survival Free from Primary Endpoint (years)
Age (years)
D. Imputed Effect of Comprehensive Therapy on Long-Term Survival
Treatment difference
Treatment difference, smoothed estimate
Upper & lower bounds, smoothed estimate
Treatment Difference in Mean Survival (years)
Age (years)


Favors
Comprehensive
(ARNI+β-blocker+MRA+SGLT2i)
Favors Limited
(ACEi/ARB+β-blocker)
CV Death or HF Hospitalization
CV Death
HF Hospitalization
All-Cause Mortality
0.0
0.2
0.4
0.6
0.8
1.0
1.2
HR (95% CI)

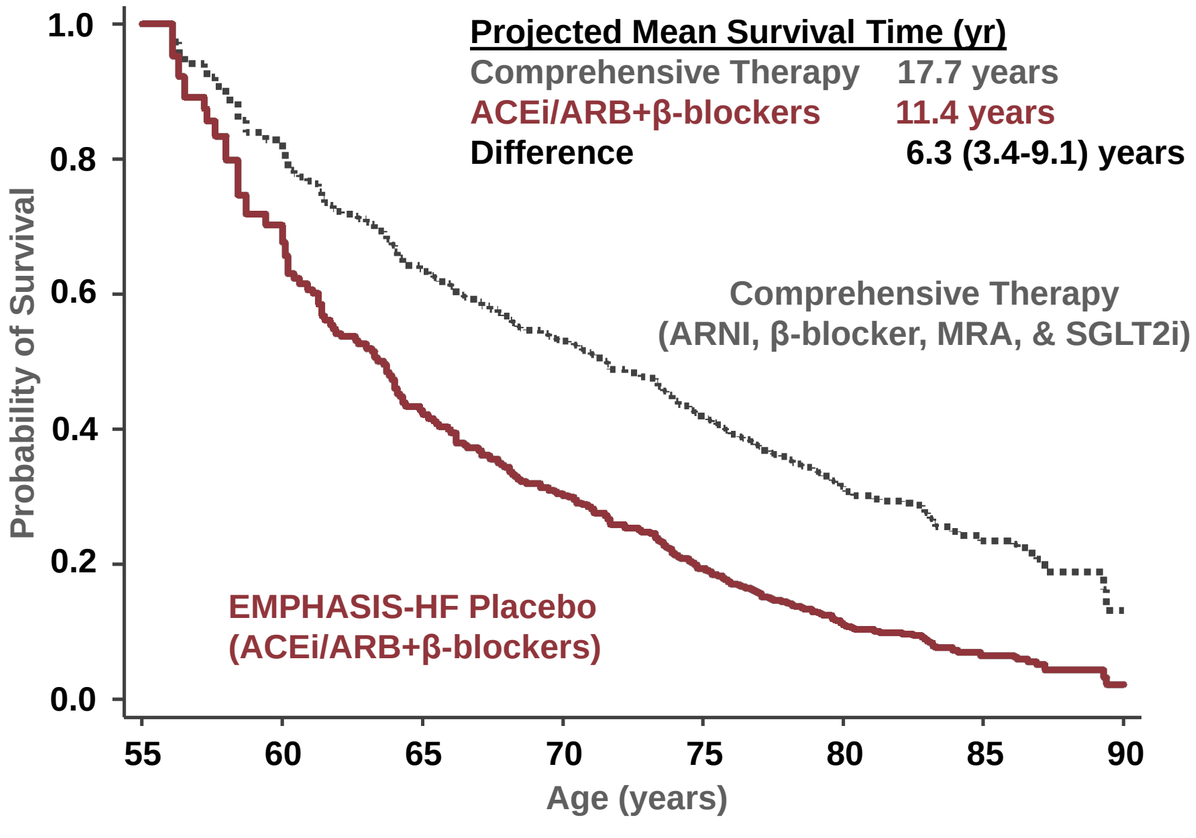
A. Projected Event-Free Survival after 55 Years



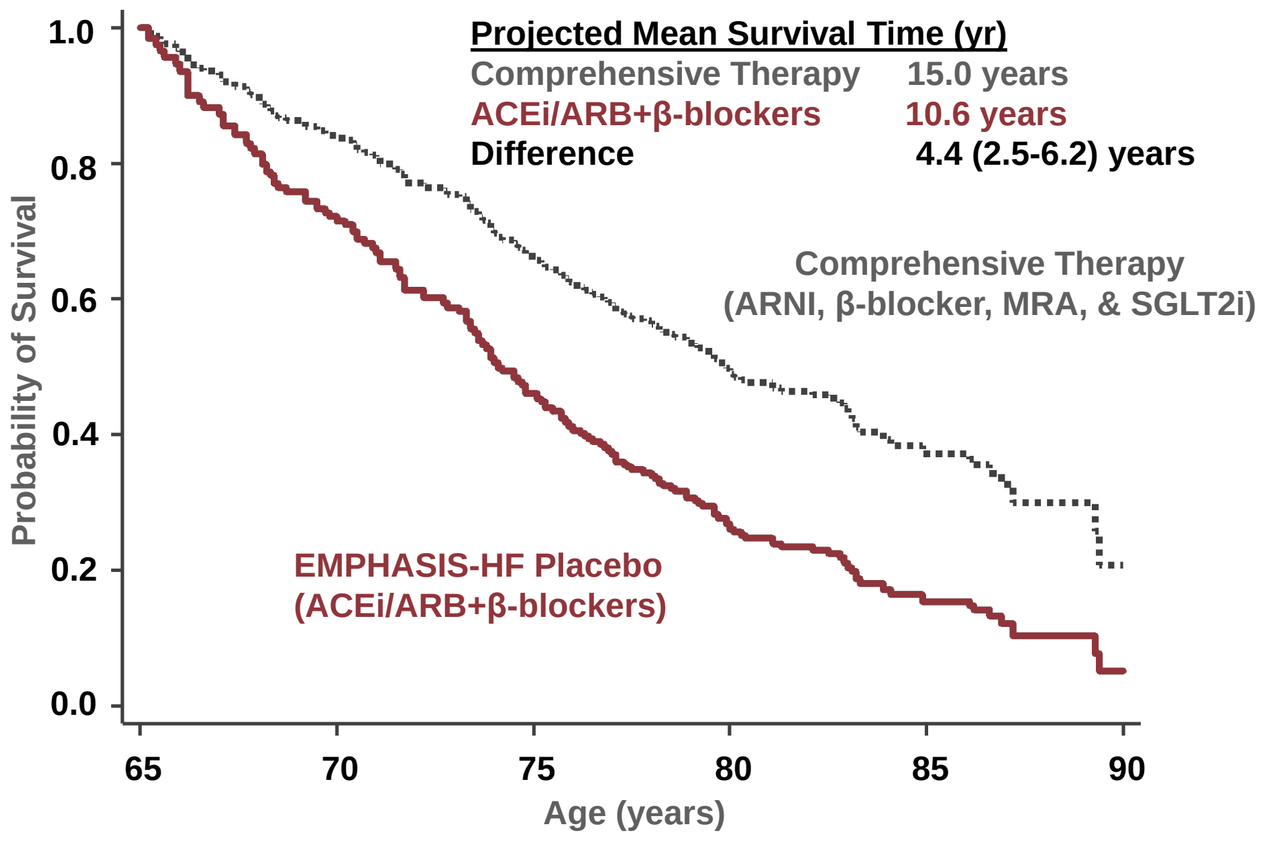
B. Projected Event-Free Survival after 65 Years



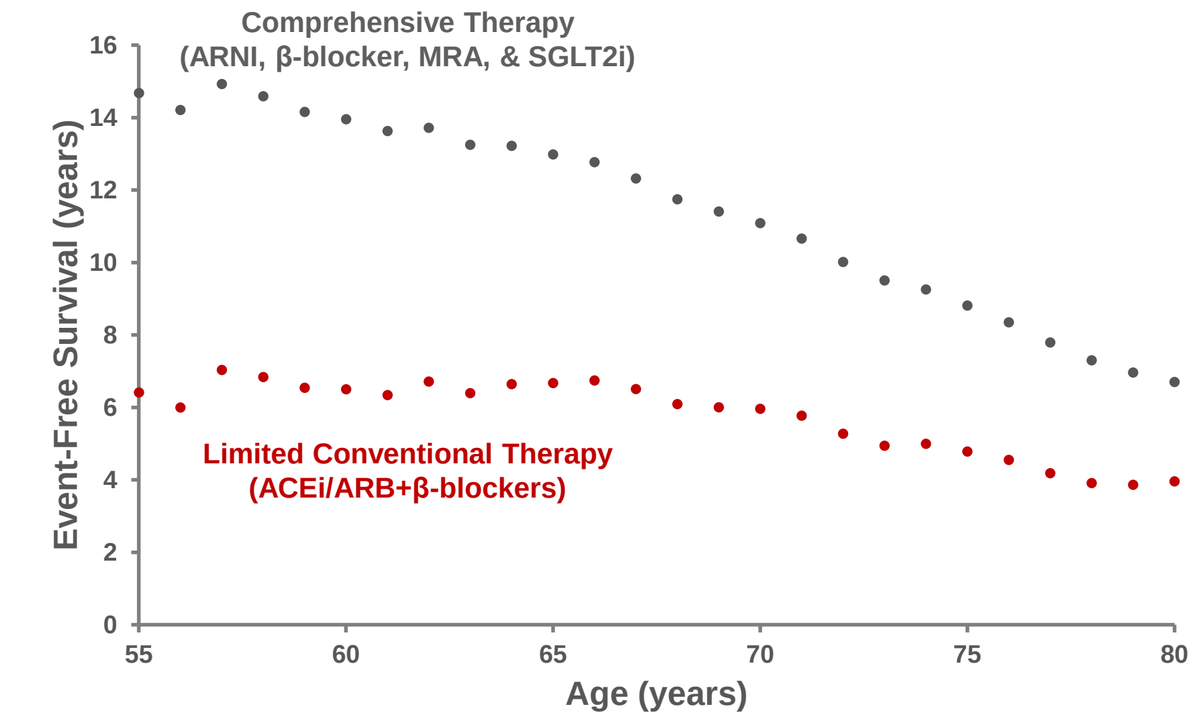
A. Projected Survival after 55 Years



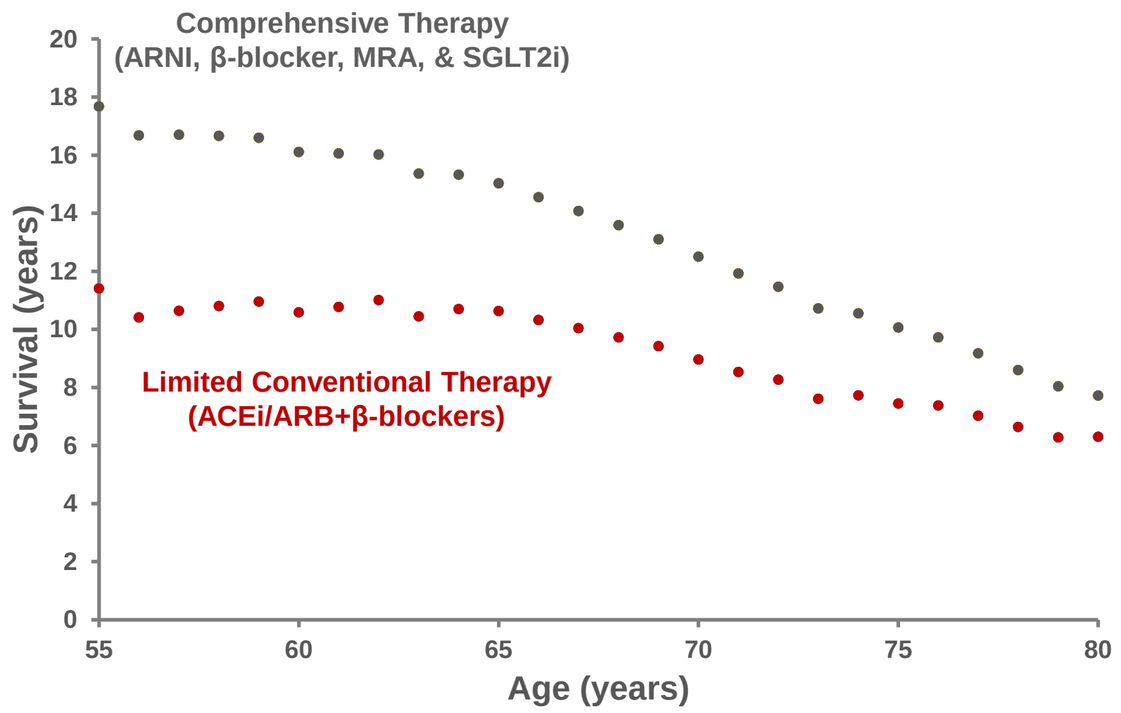
B. Projected Survival after 65 Years



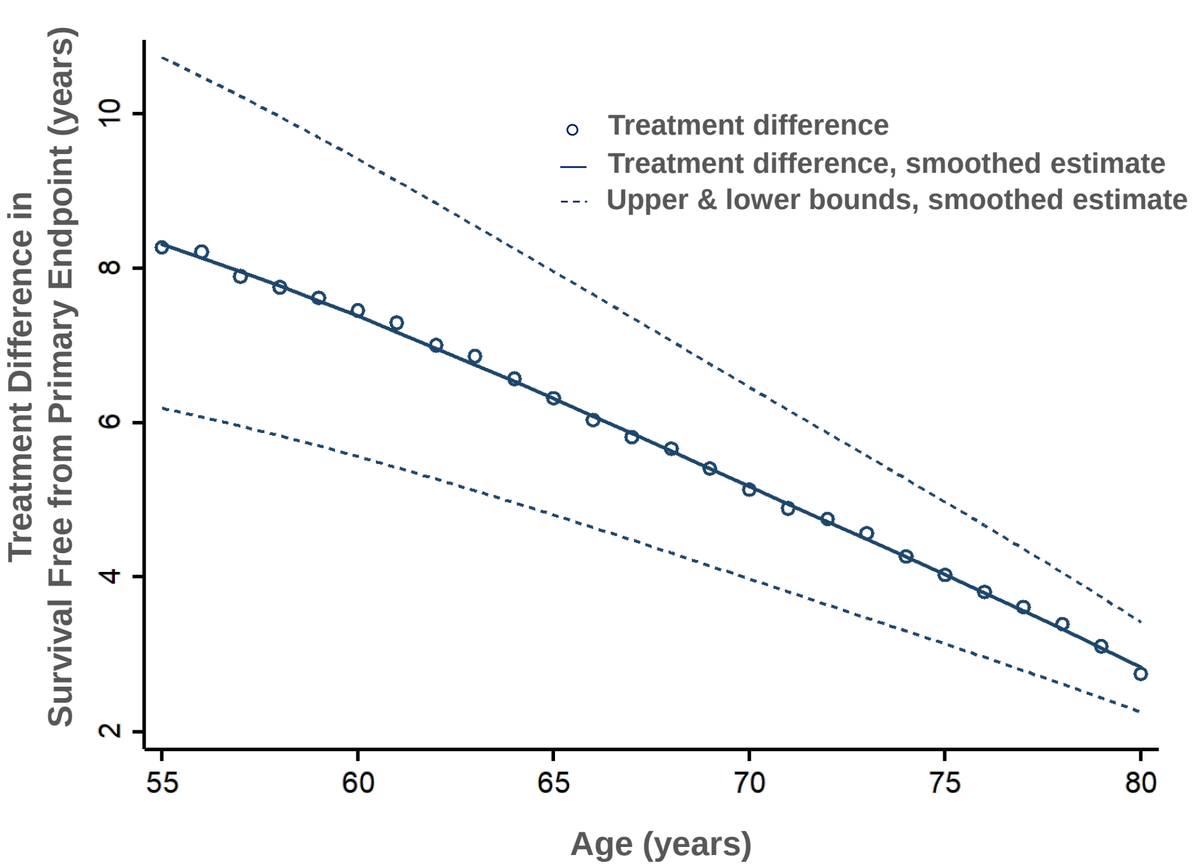
A. Estimated Survival Free from Primary Endpoint



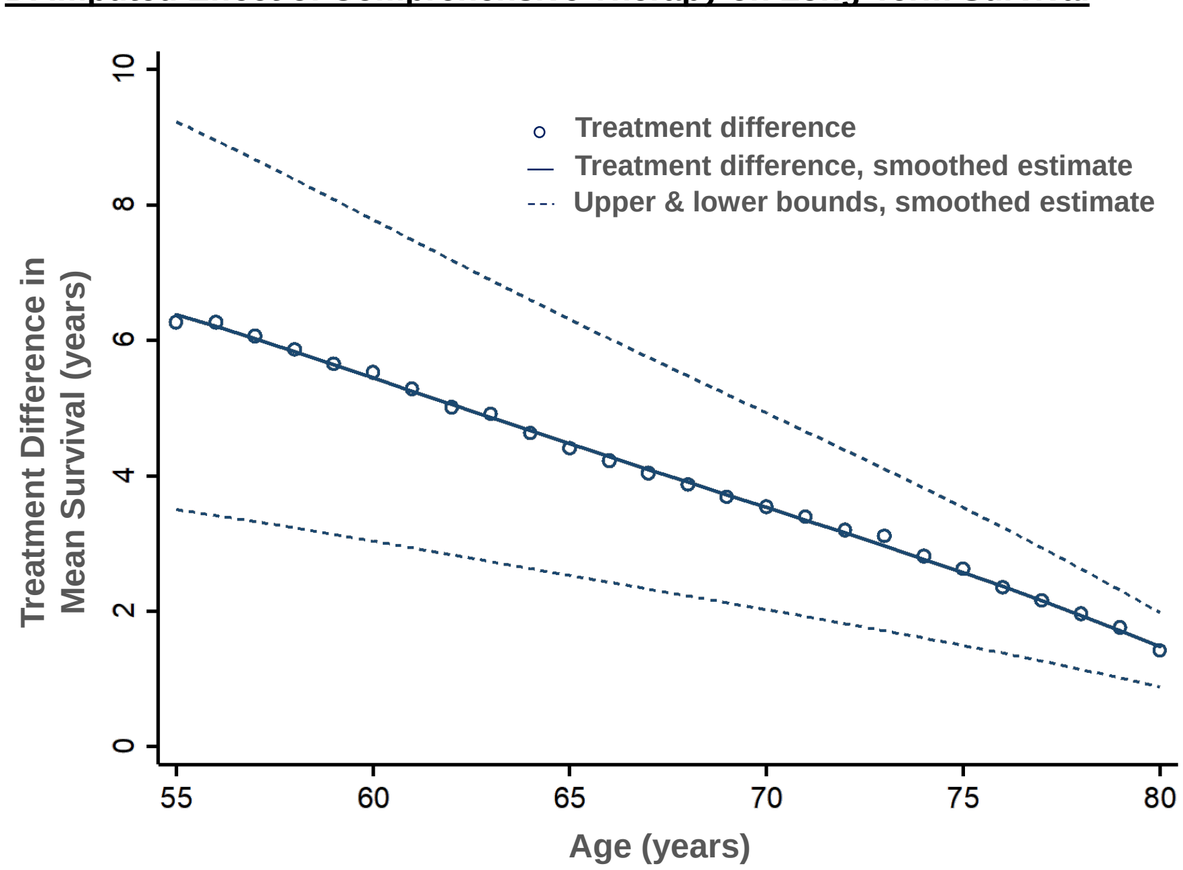
B. Estimated Residual Survival



C. Imputed Effect of Comprehensive Therapy on Event-Free Survival



D. Imputed Effect of Comprehensive Therapy on Long-Term Survival



Incremental Risk Reduction Beyond ACEi/ARB+β-Blocker